

# EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF); Scientific Opinion on Flavouring Group Evaluation 211 (FGE.211): Consideration of genotoxicity data on representatives for one alpha, beta-unsaturated ketone and three precursors from chemical subgroup 2.5 of FGE.19 by EFSA

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**SCIENTIFIC OPINION**

# Scientific Opinion on Flavouring Group Evaluation 211 (FGE.211):

# Consideration of genotoxicity data on representatives for one alpha,beta-unsaturated ketone and three precursors from chemical subgroup 2.5 of FGE.19 by EFSA[1]

## EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

## SUMMARY

The European Food Safety Authority (EFSA) asked the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (the Panel) to provide scientific advice to the Commission on the implications for human health of chemically defined flavouring substances used in or on foodstuffs in the Member States. In particular, the Panel was requested to consider the Joint FAO/WHO Expert Committee on Food Additives (the JECFA) evaluations of flavouring substances assessed since 2000, and to decide whether no further evaluation is necessary, as laid down in Commission Regulation (EC) No 1565/2000. These flavouring substances are listed in the Register, which was adopted by Commission Decision 1999/217/EC and its consecutive amendments.

The present Flavouring Group Evaluation 211 (FGE.211), corresponding to subgroup 2.5 of FGE.19, concerns one alicyclic ketone and three precursors for such a ketone. The alpha,beta-unsaturated aldehyde and ketone structures are considered by the Panel to be structural alerts for genotoxicity (EFSA, 2008b) and the data on genotoxicity previously available did not rule out the concern for genotoxicity.

The Panel has identified one substance (or its predicted metabolite) in subgroup 2.5 which will represent the other three substances in this subgroup. For one of these two substances, genotoxicity data according to the test strategy have been requested.

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1 On request from the Commission, Question No EFSA-Q-2010-01250, adopted on 4 February 2011.

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3 Acknowledgement: The Panel wishes to thank the members of the Working Group on Genotoxicity of Flavourings for the preparation of this Opinion: Vibe Beltoft, Mona-Lise Binderup, Wilfried Bursch, Angelo Carere, Riccardo Crebelli, Karl-Heinz Engel, Rainer Gürtler, John Christian Larsen, Wim Mennes, Karin Nørby and EFSA's staff member Kim Rygaard Nielsen for the preparatory work on this scientific Opinion.

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Subsequently, the Flavour Industry has performed new genotoxicity studies, and submitted *in vitro* genotoxicity data for one of the representative substances in this subgroup, 1(7),8-p-menthadien-2-yl acetate [FL-no: 09.930].

The Panel has examined these new data and concluded based on these that the *in vitro* genotoxicity data on 1(7),8-p-menthadien-2-yl acetate [FL-no: 09.930] do not indicate genotoxic potential. Accordingly the four substances in subgroup 2.5 of FGE.19 would be of no safety concern with respect to genotoxicity and will then be evaluated through the Procedue.

[FL-no: 02.100] will be evaluated in FGE.87Rev1.
[FL-no: 02.119] will be evaluated in FGE.47Rev1.
[FL-no: 07.034 and 09.930] will be evaluated in FGE.51Rev1.

**KEY WORDS**

1(7),8-p-menthadien-2-yl acetate, FL-no: 09.930, Subgroup 2.5, FGE.19, FGE.211, Genotoxicity.

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## BACKGROUND

Regulation (EC) No 2232/96 of the European Parliament and the Council (EC, 1996a) lays down a procedure for the establishment of a list of flavouring substances, the use of which will be authorised to the exclusion of all other substances in the EU. In application of that Regulation, a Register of flavouring substances used in or on foodstuffs in the Member States was adopted by Commission Decision 1999/217/EC (EC, 1999a), as last amended by Commission Decision 2009/163/EC (EC, 2009a). Each flavouring substance is attributed a FLAVIS-number (FL-number) and all substances are divided into 34 chemical groups. Substances within a group should have some metabolic and biological behaviour in common.

Substances which are listed in the Register are to be evaluated according to the evaluation programme laid down in Commission Regulation (EC) No 1565/2000 (EC, 2000a) which is broadly based on the Opinion of the Scientific Committee on Food (SCF, 1999a). For the submission of data by the manufacturer, deadlines have been established by Commission Regulation (EC) No 622/2002 (EC, 2002b).

After the completion of the evaluation programme the Union list of flavouring substances for use in or on foods in the EU shall be adopted (Article 5 (1) of Regulation (EC) No 2232/96) (EC, 1996a).

Flavouring Group Evaluation 19 (FGE.19) contains 360 flavouring substances from the EU Register being alpha, beta-unsaturated aldehydes or ketones and precursors which could give rise to such carbonyl substances via hydrolysis and / or oxidation (EFSA, 2008b).

The alpha, beta-unsaturated aldehyde and ketone structures are structural alerts for genotoxicity. The Panel noted that there were limited genotoxicity data on these flavouring substances but that positive genotoxicity studies were identified for some substances in the group.

The alpha, beta-unsaturated carbonyls were subdivided into 28 subgroups on the basis of structural similarity (EFSA, 2008b). In an attempt to decide which of the substances could go through the Procedure, a (quantitative) structure-activity relationship (Q)SAR prediction of the genotoxicity of these substances was undertaken considering a number of models (DEREKfW, TOPKAT, DTU-NFI-MultiCASE Models and ISS-Local Models, (Gry et al., 2007)).

The Panel noted that for most of these models internal and external validation has been performed, but considered that the outcome of these validations was not always extensive enough to appreciate the validity of the predictions of these models for these alpha, beta- unsaturated carbonyls. Therefore, the Panel considered it inappropriate to totally rely on (Q)SAR predictions at this point in time and decided not to take substances through the procedure based on negative (Q)SAR predictions only.

The Panel took note of the (Q)SAR predictions by using two ISS Local Models (Benigni & Netzeva, 2007a; Benigni & Netzeva, 2007b) and four DTU-NFI MultiCASE Models (Gry et al., 2007; Nikolov et al., 2007) and the fact that there are available data on genotoxicity, *in vitro* and *in vivo*, as well as data on carcinogenicity for several substances. Based on these data the Panel decided that 15 subgroups (1.1.1, 1.2.1, 1.2.2, 1.2.3, 2.1, 2.2, 2.3, 2.5, 3.2, 4.3, 4.5, 4.6, 5.1, 5.2 and 5.3) (EFSA, 2008b) could not be evaluated through the Procedure due to concern with respect to genotoxicity. Corresponding to these subgroups, 15 Flavouring Group Evaluations (FGEs) were established, FGE.200, 204, 205, 206, 207, 208, 209, 211, 215, 219, 221, 222, 223, 224 and 225).

For 11 subgroups the Panel decided, based on the available genotoxicity data and (Q)SAR predictions, that a further scrutiny of the data should take place before requesting additional data from the Flavouring Industry on genotoxicity. These subgroups were evaluated in FGE.201, 202, 203, 210, 212, 213, 214, 216, 217, 218 and 220. For the substances in FGE.202, 214 and 218 it was concluded that a genotoxic potential could be ruled out and accordingly these substances will be evaluated using the Procedure. For all or some of the substances in the remaining FGEs, FGE.201. 203, 210, 212, 213, 216, 217 and 220 the genotoxic potential could not be ruled out.

To easy the data retrieval of the large number of structurally related alpha,beta-unsaturated substances in the different subgroups for which additional data are requested, EFSA has worked out a list of representative substances for each subgroup (EFSA, 2008bc). Likewise an EFSA genotoxicity expert group has worked out a test strategy to be followed in the data retrieval for these substances (EFSA, 2008bb).

The Flavouring Industry has been requested to submit additional genotoxicity data according to the list of representative substances and test strategy for each subgroup.

The Flavouring industry has now submitted additional data and the present FGE concerns the evaluation of these data requested on genotoxicity.

## TERMS OF REFERENCE

The European Commission requests the European Food Safety Authority to carry out an evaluation of the data on 1(7),8-p-menthadien-2-yl acetate (mixture of (E) and (Z) isomers) [FL-no: 09.930], in accordance with Commission Regulation (EC) No 1565/2000. Depending on the outcome, the Europen Commission asks EFSA to evaluate all the substances of the corresponding subgroup (FGE.19 subgroup 2.5) through the Procedure.

## ASSESSMENT

### 1. Presentation of the substances in the JECFA Flavouring Group

### 1.1. Description

The present Flavouring Group Evaluation 211 (FGE.211), corresponding to subgroup 2.5 of FGE.19, concerns one alicyclic ketone and three precursors for such a ketone. The four substances under consideration in the present evalution are listed in Table 1.

Three of the substances have previously been evaluated by the JECFA, a summary of their current evalution status by the JECFA and the outcome of this consideration is presented in Table 2 (JECFA, 2003a; JECFA, 2006a).

The alpha,beta-unsaturated aldehyde and ketone structures are considered alerts for genotoxicity (EFSA, 2008b) and the data on genotoxicity previously available did not rule out the concern for genotoxicity.

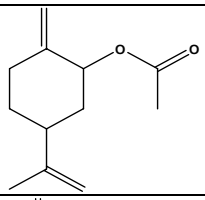
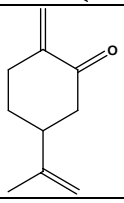
### 1.2. Representative substances for subgroup 2.5

The Panel has identified one substance (or its predicted metabolite) in subgroup 2.5 which will represent the other three substances this subgroup (EFSA, 2008bc). For one of these two substances genotoxicity data according to the test strategy (EFSA, 2008bb) have been requested. The representative substances are shown in table 1.1.

**TABLE 1.1 REPRESENTATIVE SUBSTANCES FOR SUBGROUP 2.5 OF FGE.19**

| FL-no<br>JECFA-no | Subgroup | EU Register name | Structural formula | FEMA no<br>CoE no<br>CAS no |
|---|---|---|---|---|

**TABLE 1.1 REPRESENTATIVE SUBSTANCES FOR SUBGROUP 2.5 OF FGE.19**

| FL-no<br>JECFA-no | Subgroup | EU Register name | Structural formula | FEMA no<br>CoE no<br>CAS no |
|---|---|---|---|---|
| 09.930<br>1098 | 2.5 | 1(7),8-p-Menthadien-2-yl acetate (mixture of (E) and (Z) isomers) |  | -<br>-<br>71660-03-2 |
| Non-Register | 2.5 | 1(7),8-p-menthadien-2-one (Cyclohexanone, 2-methylene-5-(1-methylethenyl)-) |  | -<br>-<br>79367-79-6 |

## 2. Additionally submitted genotoxicity data on representative substances of subgroup 2.5

### Introduction

The Industry has submitted data concerning genotoxicity studies for the one representative substance for this subgroup, 1(7),8-p-menthadien-2-yl acetate [FL-no: 09.930] (structurally related to 1(7),8-p-menthadien-2-one).

### 2.1. *In vitro* data

The newly available data comprise a bacterial reverse mutation assay and an *in vitro* micronucleus assay with human peripheral blood lymphocytes. The genotoxicity assays have been performed on a commercial mixture of the representative substance 1(7),8-p-menthadien-2-yl acetate and a positional isomer, carvyl acetate. Carvyl acetate can be hydrolysed followed by oxidation to carvone, which has been evaluated by EFSA in FGE.212 (EFSA, 2009ai) and NTP (NTP, 1990b) as non-genotoxic. The highest concentration of d-carvone that could be tested without cytotoxicity was 333 µg/plate (Mortelmans et al., 1986), i.e. the cytotoxicity was in the same range as observed for the mixture of 1(7),8-p-menthadien-2-yl acetate/carvyl acetate. The Panel concluded that testing the commercial mixture of 1(7),8-p-menthadien-2-yl acetate/carvyl acetate for genotoxicity allows the evaluation of the genotoxic potential of 1(7),8-p-menthadien-2-yl acetate. The concentrations reported in Table 3 are for the mixture of substances.

#### 2.1.1. Bacterial Reverse Mutation Assay

***1(7),8-p-menthadien-2-yl acetate/carvyl acetate*** was tested for mutagenic activity according to OECD guideline 471 and in compliance with GLP (Beevers, 2010a). The test material exhibited a marked toxicity as indicated by thinning of the background lawn, reduced revertant counts and complete killing of test bacteria. However, the Panel considered the remaining number of concentrations without signs of toxicity sufficient to draw a conclusion on mutagenicity in this system (for details see table 3).

Overall, the Panel concluded that there was no evidence of mutagenic activity of 1(7),8-p-menthadien-2-yl acetate/carvyl acetate at concentrations up to those causing bactericidal effects.

#### 2.1.2. *In vitro* Micronucleus Test

***1(7),8-p-menthadien-2-yl acetate/carvyl acetate*** was tested for induction of micronulei in human peripheral blood lymphocytes according to OECD guideline 487 and in compliance with GLP (Whitwell, 2010b). The Panel considered that acceptable levels of cytotoxicity as judged upon the replication index were achieved at the top concentrations (for details see Table 3).

Overall, the Panel concluded that no evidence of chromosomal damage or aneuploidy was observed by increased levels of micronucleated binucleate cells (MNBN) in the presence or absence of S9 metabolic activation.

A summary of the *in vitro* genotoxicity data is given in Table 3.

### 2.2. *In vivo* data

Based on the *in vitro* data available no *in vivo* data are needed.

### 2.3. Discussion of Mutagenicity/Genotoxicity Data

The commercial mixture of the representative substance 1(7),8-p-menthadien-2-yl acetate and a positional isomer, carvyl acetate was tested for all three genetic endpoints: gene mutations, structural and numerical chromosomal aberrations. The test material did not induce gene mutations in bacteria and was not clastogenic and/or aneugenic in mammalian cells *in vitro*. Although this commercial mixture was cytotoxic at high concentrations. the remaining concentrations without signs of toxicity provide a valid data set.

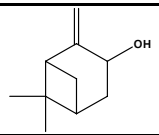
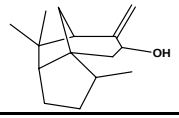
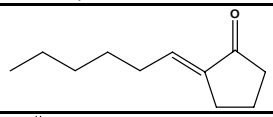
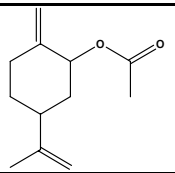
## 3. Conclusion

The *in vitro* genotoxicity data on the commercial mixture of the representative substance 1(7),8-p-menthadien-2-yl acetate [FL-no: 09.930] and a positional isomer, carvyl acetate do not indicate genotoxic potential. Accordingly the four substances in subgroup 2.5 of FGE.19 would be of no safety concern with respect to genotoxicity and will then be evaluated through the Procedue.

[FL-no: 02.100] will be evaluated in FGE.87Rev1.
[FL-no: 02.119] will be evaluated in FGE.47Rev1.
[FL-no: 07.034 and 09.930] will be evaluated in FGE.51Rev1.

## TABLE 1: SPECIFICATION SUMMARY OF THE SUBSTANCES IN THE FLAVOURING GROUP EVALUATION 211 (JECFA, 2002D; JECFA, 2005B)

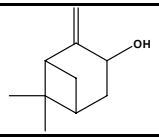
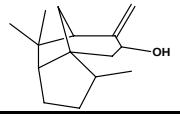
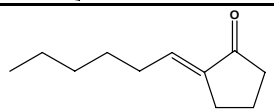
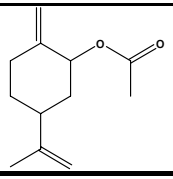
**Table 1: Specification Summary of the Substances in the present group (JECFA, 2002d; JECFA, 2005b)**

| FL-no<br>JECFA-no | EU Register name | Structural formula | FEMA no<br>CoE no<br>CAS no | Phys.form<br>Mol.formula<br>Mol.weight | Solubility 1)<br>Solubility in ethanol 2) | Boiling point, °C 3)<br>Melting point, °C<br>ID test<br>Assay minimum | Refrac. Index 4)<br>Spec.gravity 5) |
|---|---|---|---|---|---|---|---|
| 02.100<br>1403 | Pinocarveol |  | 3587<br>10303<br>5947-36-4 | Liquid<br>$C_{10}H_{16}O$<br>152.24 | Insoluble<br>Soluble | 210<br><br>NMR<br>95 % | 1.445-1.451<br>0.977-0.983 |
| 02.119 | Cedrenol |  | 10189<br>28231-03-0 | Solid<br>$C_{15}H_{24}O$<br>220.35 | Practically insoluble or insoluble<br>Soluble | 98 (0.27 hPa)<br>128<br>MS<br>95 % | n.a.<br>n.a. |
| 07.034<br>1106 | 2-Hexylidenecyclopentan-1-one |  | 2573<br>167<br>17373-89-6 | Liquid<br>$C_{11}H_{18}O$<br>166.26 | | 240<br><br>NMR<br>98 % | 1.477-1.484<br>0.907-0.914 |
| 09.930<br>1098 | 1(7),8-p-Menthadien-2-yl acetate (mixture of (E) and (Z) isomers) |  | 71660-03-2 | Liquid<br>$C_{12}H_{18}O_2$<br>194.27 | | 77-79 (0.1 hPa)<br><br>IR NMR MS<br>95 % | 1.473-1.479<br>0.964-0970 |

1) Solubility in water, if not otherwise stated.
2) Solubility in 95 % ethanol, if not otherwise stated.
3) At 1013.25 hPa, if not otherwise stated.
4) At 20°C, if not otherwise stated.
5) At 25°C, if not otherwise stated.

## TABLE 2: CURRENT SAFETY EVALUATION STATUS APPLYING THE PROCEDURE (BASED ON INTAKES CALCULATED BY THE MSDI APPROACH) (JECFA, 2003A; JECFA, 2006A)

**Table 2: Summary of Safety Evaluation of the JECFA substances in the present group (JECFA, 2003a; JECFA, 2006a)**

| FL-no<br>JECFA-no | EU Register name | Structural formula | EU MSDI 1)<br>US MSDI<br>(µg/*capita*/day) | Class 2)<br>Evaluation procedure path 3) | JECFA Outcome on the named compound [4) or 5)] | EFSA conclusion on the named compound ( genotoxicity) |
|---|---|---|---|---|---|---|
| 02.100<br>1403 | Pinocarveol |  | 0.012<br>0.01 | Class I<br>A3: Intake below threshold | 4) | Evaluated in FGE.211, genotoxicity concern could be ruled out.. |
| 02.119 | Cedrenol |  | 34 | Class I<br>No evaluation | Not evaluated by JECFA | Evaluated in FGE.211, genotoxicity concern could be ruled out.. |
| 07.034<br>1106 | 2-Hexylidenecyclopentan-1-one |  | 0.24<br>0.01 | Class II<br>A3: Intake below threshold | 4) | Evaluated in FGE.211, genotoxicity concern could be ruled out.. |
| 09.930<br>1098 | 1(7),8-p-Menthadien-2-yl acetate (mixture of (E) and (Z) isomers) |  | 0.61<br>0.6 | Class II<br>A3: Intake below threshold | 4) | Evaluated in FGE.211, genotoxicity concern could be ruled out.. |

1) EU MSDI: Amount added to food as flavour in (kg / year) x 10E9 / (0.1 x population in Europe (= 375 x 10E6) x 0.6 x 365) = µg/capita/day.
2) Thresholds of concern: Class I = 1800 µg/person/day, Class II = 540 µg/person/day, Class III = 90 µg/person/day.
3) Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.
4) No safety concern based on intake calculated by the MSDI approach of the named compound.
5) Data must be available on the substance or closely related substances to perform a safety evaluation.

## TABLE 3: GENOTOXICITY (*IN VITRO*)

**Table 3: Summary of Additionally submitted genotoxicity data on the representative substance of subgroup 2.5**

| FL-no JECFA-no | Chemical Name | Test System | Test Object | Concentrations of Substance and Test Conditions | Result | Reference | Comments |
|---|---|---|---|---|---|---|---|
| 09.930 1098 | 1(7),8-*p*- Menthadien-2-yl acetate | Reverse Mutation | *S. typhimurium* TA98, TA100, TA1535, TA1537 and TA 102 | 1.6*, 8*, 40*, 200, 1000 and 5000 µg/plate [1,2] | Negative | (Beevers, 2010a) | * concentration without cytotoxicity |
| | | | *S. typhimurium* TA98, TA1535 and TA1537 | 15.6*, 31.3*, 62.5*, 125, 250 and 500 µg/plate [2,3] | Negative | | |
| | | | *S. typhimurium* TA100 and TA 102 | 78.1*, 156.3*, 312.5, 625, 1250 and 2500 µg/plate [2,3] | Negative | | |
| | | | *S. typhimurium* TA98 and TA100 | 156.3*, 312.5, 625, 1250, 2500 and 5000 µg/plate [4,5] | Negative | | |
| | | | *S. typhimurium* TA1535, TA1537 and TA 102 | 78.1*, 156.3*, 312.5, 625, 1250 and 2500 µg/plate [4,5] | Negative | | |
| | | | *S. typhimurium* TA100 | 25*, 50*, 100*, 200 and 400 µg/plate [2,3] | Negative | | |
| | | | *S. typhimurium* TA98 | 50*, 100*, 200*, 400 and 800 µg/plate [4,5] | Negative | | |
| | | | *S. typhimurium* TA100, TA1535, TA1537 and TA 102 | 25*, 50*, 100*, 200 and 400 µg/plate [4,5] | Negative | | |
| | | Micronucleus induction | Human peripheral blood lymphocytes | 80, 90 and 110 µg/ml [3,6]; 200, 300 and 400 µg/ml [5,6] | Negative | (Whitwell, 2010b) | 50 to 65 % cytotoxicity at top concentrations |
| | | | | 20, 50, 80 and 100 µg/ml [3,7] | Negative | | |

[1] With and without S9 metabolic activation.
[2] Plate incorporation method.
[3] Without S9 metabolic activation.
[4] Pre-incubation method.
[5] With S9 metabolic activation.
[6] 3-hour incubation with 21-hours recovery period.
[7] 24-hour incubation with no recovery period.

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Benigni R and Netzeva T, 2007a. Report on a QSAR model for prediction of genotoxicity of alpha,beta-unsaturated aldehydes in S. typhimurium TA 100 and its application for predictions on alpha,beta-unsaturated aldehydes in Flavouring Group Evaluation 19 (FGE.19). Unpublished report submitted by FLAVIS Secretariat to EFSA.

Benigni R and Netzeva T, 2007b. Report on a QSAR model for prediction of genotoxicity of alpha,beta-unsaturated ketones in *S. typhimurium* TA 100 and its application for predictions on alpha,beta-unsaturated aldehydes in Flavouring Group Evaluation 19 (FGE.19). Unpublished report submitted by FLAVIS Secretariat to EFSA.

EC, 1996a. Regulation No 2232/96 of the European Parliament and of the Council of 28 October 1996. Official Journal of the European Communities 23.11.1996, L 299, 1-4.

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## ABBREVIATIONS

| | |
|---|---|
| CAS | Chemical Abstract Service |
| CEF | Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids |
| CoE | Council of Europe |
| EFSA | The European Food Safety Authority |
| EU | European Union |
| FAO | Food and Agriculture Organization of the United Nations |
| FGE | Flavouring Group Evaluation |
| FLAVIS (FL) | Flavour Information System (database) |
| ID | Identity |
| IR | Infrared spectroscopy |
| JECFA | The Joint FAO/WHO Expert Committee on Food Additives |
| MNBN | MicroNucleated BiNucleate cells |
| MS | Masse spectra |
| MSDI | Maximised Survey-derived Daily Intake |
| mTAMDI | Modified Theoretical Added Maximum Daily Intake |
| NMR | Nuclear Magnetic Resonance |
| No | Number |
| NOAEL | No observed adverse effect level |
| NTP | National Toxicology Program |
| OECD | Organisation for Economic Co-operation and Development |
| (Q)SAR | (Quantitative ) Structure Activity Relationship |
| SCF | Scientific Committee on Food |
| WHO | World Health Organisation |